CONDENSATION OF 2-TOSYLAMINOINDOLE WITH AROMATIC ALDEHYDES

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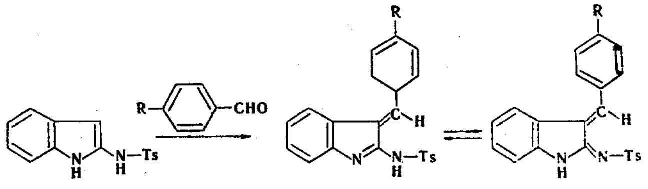
The condensation of 2-tosylaminoindole and 1-methyl-2-tosylaminoindoline with aromatic aldehydes gives primarily trans-3-arylidene derivatives, which exist in two tautomeric forms in solution.

Depending on the acidity of the medium, 1-alkyl-2-aminoindoles react with aromatic aldehydes to give Schiff bases, 3-arylidene derivatives, or substituted indolo[2,3-b]-α-carbolines [1, 2].

It was found that 2-tosylaminoindole (I) on heating with benzaldehyde in an alcohol solution of acetic acid gives a yellow crystalline substance with the composition $C_{22}H_{18}N_2O_2S$, which corresponds to the product of condensation of one 2-tosylaminoindole molecule with one aldehyde molecule, to which one can assign structure II.

The signal of the 3-H proton of the indole ring is absent in the PMR spectrum of the product (in $CDCl_3$) recorded with a Cameca-250 spectrometer, but there is a broad signal at 10.24 ppm (1H) of the proton of an N−H group, a singlet at 8.12 ppm of a vinyl proton of a benzylidene group, and an isolated doublet (2H) of a tosyl group at 7.8 ppm with J = 8 Hz; the signals of the remaining 11 aromatic protons lie at 6.92-7.62 ppm, and the singlet of a CH_3 group is found at 2.4 ppm.

These data and the IR spectral data [absorption in the C=N (1640 cm^{-1}) and N−H (3280 cm^{-1}) regions] are in good agreement with structure IIa.



I IIa-f IIIa-f

II, III a R=H; b R=N(CH$_3$)$_2$; c R=OCH$_3$; d R=CH(CH$_3$)$_2$; e R=Cl; f R=NO$_2$

We carried out this reaction in dimethyl sulfoxide (DMSO), alcohol, alcohol−triethylamine, alcoholic alkali, pyridine, acetic acid, and alcohol saturated with hydrogen chloride. However, the chief product in all cases was IIa. Compounds IIb-f were similarly obtained (Table 1).

3-Benzylideneoxindole (VII) of known structure [9] is formed when IIa is subjected to prolonged refluxing in an alcohol solution of HBr or HCl.

The molecular ion peaks in the mass spectra of II have low intensities (0.9-10%), i.e., the molecule displays low stability with respect to electron impact. The chief process in the fragmentation of the molecular ions was cleavage of the C−S bond to give the maximum ion $C_7H_7^+$ (m/e 91). In addition, another characteristic process is elimination of the tosyl group to give intense F_1 ions $(M-155)^+$, which then eliminate a hydrogen atom and, probably, form a rearranged benzo-α-carboline ion [F_2, $(M-156)^+$]. Because

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TABLE 1. 3-Arylidene-1-tosylaminoindoles

II	R	mp, °C	IR spectrum (mineral oil), cm^{-1}		PMR ($CDCl_3$), ppm			UV spectrum ($CHCl_3$)		Yield, %
			C=N	N-H	CH_3	=CH-	aromatic	λ_{max}	lg ε	
a	H	202—203	1640	3280	2,74	8,1	7,2—8.0	272 346 Inflection 410	4,44 4,13 3,83	87
b	$N(CH_3)_2$	227—228	1655	3280	2,80 3,50 $N(CH_3)_2$	8,23	7,1—8,15	264 329 475	4,28 3,66 4,32	83
c	NO_2	233—234	1610	3320	2.76	8,03	7,5—7,8	287 354 Inflection 412	4,68 4,26 3,85	91
d	OCH_3	208—210	1640	3280	2,7 4,2 (OCH_3)	8,20	7,2—8,1	270 373 Inflection 424	4,10 4,24 4,04	80
e	Cl	184—186	1660	3280	2,7	8,01	7,4—7,9	280 350 Inflection 410	4,18 4,24 3,94	84
f	$CH(CH_3)_2$	205—206	1630	3295	2,8 3,34 $CH(CH_3)_2$	8,08	7,5—7,9	270 355 Inflection 395	4,34 4,20 4,0	90

TABLE 2. Intensities of the Principal Ions (in % relative to I_{max})

Fragment	Compound					
	P_a	P_b	P_c	P_d	P_e	P_f
	R					
	H	$N(CH_3)_2$	OCH_3	$CH(CH_3)_2$	Cl	NO_2
F_1	81,5	13,0	4,0	15,0	23,4	5,05
F_2	21,2	24,0	—	2,3	4,6	4,9
F_3	—	2,0	4,2	6,9	15,7	19,0
F_4	9,6	10,2	12,8	23,6	17,3	21,0
M^+	3,3	10,0	0,79	3,6	5,66	3,05

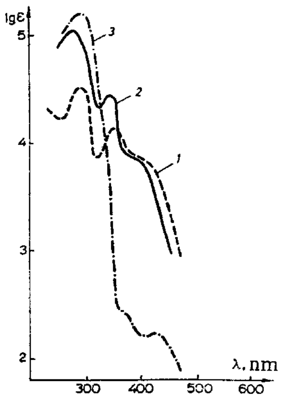


Fig. 1. UV absorption spectra (in chloroform): 1) 3-benzylidene-2-tosylaminoindole; 2) 3-benzylidene-2-(N-methyltosylamino)indole; 3) 3-benzyl-idene-2-tosylamino-1-methylindoline.

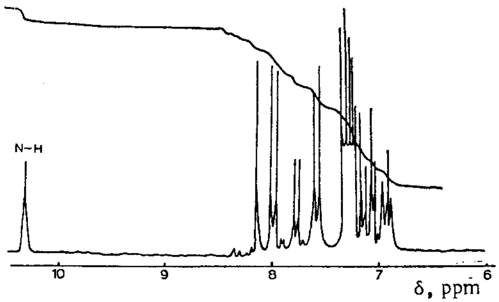
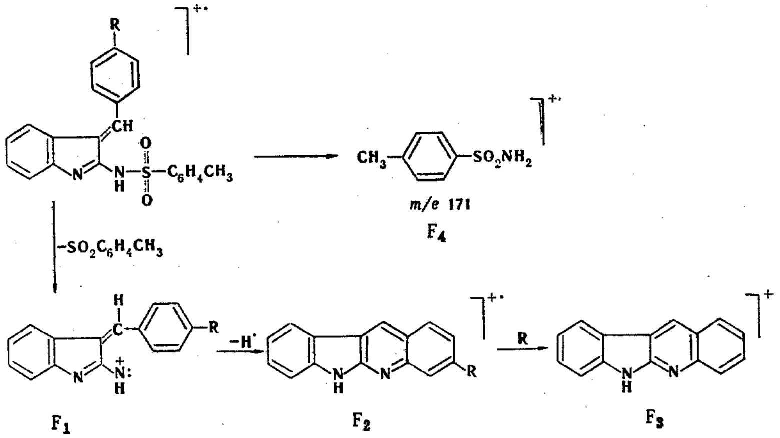


Fig. 2. PMR spectrum of 3-(p-isopropylbenzylidene)-2-tosylaminoindole (in deuterochloroform) recorded with a Cameca-250 spectrometer.

of the high stability of the carboline system with respect to electron impact, the F_2 ions have high intensities and undergo subsequent fragmentation only to give F_3 ions by splitting out of substituent R [4]. In addition, the formation of an intense ion with m/e 171, which apparently has a tosylamide composition, is characteristic for all II.

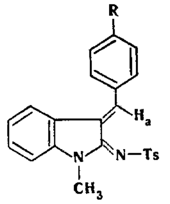


Thus the fragmentation of the products of condensation of 2-tosylaminoindole is in agreement with the proposed structure (IIa-f) of the compounds (Table 2).

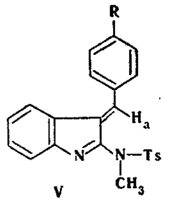
The UV spectra of chloroform and DMSO solutions of II and III have characteristic absorption bands at 260-280 and 340-380 nm, i.e., with respect to the position of the absorption maxima and the type of curve they are similar to the spectra of 3-arylidene-2-aminoindoles and 3-arylideneoxindoles [2, 3].

One can conceive of the existence of three tautomeric forms for the free 2-aminoindole base. Kebrle and Hoffmann [6], on the basis of UV and IR spectroscopic data and the results of measurements of the pK_a value, established that, of these tautomeric forms, the indolenine form is predominant. Later, Bailey and Buckley [7] and Harman and co-workers [8] reported that the equilibrium of amines I in deuterated chloroform is characterized by a tautomer ratio close to 1 : 1.

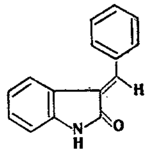
The 3-arylidene derivatives that we obtained in this research may exist in two forms – II and III. A comparison of the UV spectra of the synthesized compounds with the spectra of model compounds methylated at one or the other nitrogen atom (IV and V), i.e., fixed III and II forms, respectively, provides evidence that the investigated substances exist primarily in the II form in chloroform and DMSO solutions (Fig. 1). The 3-(p-dimethylaminobenzylidene) derivative of 2-tosylaminoindole, which exists primarily in the IIIb form in chloroform solution [UV spectrum, λ_{max} ($CHCl_3$): 264, 329, and 476 nm (log ε 4.28, 3.66, and 4.32); IR spectrum ($CHCl_3$): C=N 1615, 1640 cm^{-1}; N–H 3380 cm^{-1}], constitutes an exception to this, and this is evidently associated with specific solvation by the solvent.



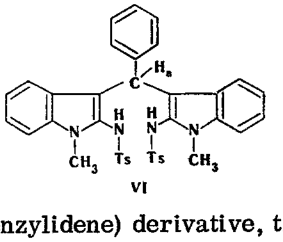
IV



V



VII



VI

With the exception of the 3-(p-nitrobenzylidene) derivative, the investigated compounds also exist in the II form in the crystalline state, inasmuch as intense bands of stretching vibrations of C=N (1630-1640 cm^{-1}) and N–H (3280-3295 cm^{-1}) groups are observed in their IR spectra (in mineral oil). Based on the data from the IR spectra of model compounds IV and V and their 3-arylideneoxindole analogs [3], structure III has C=N (1600-1620 cm^{-1}) and N–H (3310-3340 cm^{-1}) absorption bands.

Bailey and Buckley [5] have reported that primarily a compound of the VI type is formed in the reaction of 1-methyl-2-arenesulfamidoindoles with aromatic aldehydes, but, depending on the acidity of the medium, an admixture of a compound of the IV type may also be formed. Our experiments with unmethylated I always gave the 3-arylidene derivative, in which contamination by VI could be detected only chromatographically and the contaminant was easily separated by crystallization.

A trans configuration can be assigned to the compounds obtained in this research on the basis of a comparison of the physicochemical data with the data recorded for 3-benzylidene oxindoles (VII) with established configurations [3]. Analogous compounds obtained from 1-methyl-2-arenesulfamidoindoles and aromatic aldehydes [5] have a configuration of this sort [5].

The PMR spectra of deuterochloroform solutions of IIa-f, recorded with a Cameca-250 spectrometer, which makes it possible to determine the percentage of impurities up to 1%, indicate the existence also of another isomeric form, and its percentage varies from 3 to 9%. For example, 3-(p-isopropylbenzylidene)-2-tosylaminoindole contains 3% of the other isomer (Fig. 2). The PMR spectra of IIa-d recorded with a Varian T-60 spectrometer do not reveal contamination by the second isomer, and in the case of IVb one observes the presence of different isomeric forms in the spectra recorded even with this spectrometer. This was also demonstrated by means of two-dimensional chromatography with the use of the same solvent system [benzene–ethyl acetate (4:1)] in both directions. The isomer (82:18%) was determined by means of the PMR spectrum by comparison of the intensities of the corresponding signals.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions and chloroform solutions of the compounds were recorded with IKS-22 and UR-10 spectrometers. The UV spectra of chloroform, alcohol, and DMSO solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra of deuterochloroform and trifluoroacetic acid solutions were recorded with Varian T-60, X-100, and Cameca-250 spectrometers with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with a system for direct introduction of the sample into the ion source (50 eV, 230°).

3-Benzylidene-2-tosylaminoindoles. A mixture of 1.75 mmole of 2-tosylaminoindoles and 3 mmole of freshly distilled or recrystallized aromatic aldehyde was stirred and refluxed for 4 h in 5 ml of absolute ethanol and 3 ml of glacial acetic acid, after which the mixture was cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and recrystallized from methanol. The yield and physical constants of 3-benzylidene-2-(p-tosylaminoindoles) IIa-f are given in Table 1.

3-Benzylidene-2-(N-methyltosylamino)indole. Similarly, 0.095 g of colorless crystals of V, with mp 200-203° and R_f 0.44 [Silufol; benzene–methanol (5:1)], was obtained from 0.2 g (0.62 mmole) of 2-(N-methyltosylamino)indole and 0.25 g (2 mmole) of freshly distilled benzaldehyde after heating for 20 h on a water bath. UV spectrum ($CHCl_3$): λ_{max} 278 and 340 nm (log ε 5.04 and 4.40); inflection λ_{av} 380 nm (log ε 3.83). PMR spectrum ($CDCl_3$): 2.8 (3H, s, $TsCH_3$), 3.44 (3H, s, NCH_3), 7.3-8.1 (13H, m, aromatic protons), and 8.56 (1H, s, H_a). Found: C 70.7; H 5.0; N 6.9%. $C_{23}H_{20}N_2O_2S$. Calculated: C 71.2; H 5.2; N 7.2%.

Reaction of 1-Methyl-2-tosylaminoindole with Benzaldehyde and p-Dimethylaminobenzaldehyde. A) 3-Benzylidene-2-tosylimino-1-methylindoline (IVa). A similar procedure was used to prepare the following compounds. The method gave 0.22 g of IVa with mp 215-218° and R_f 0.52 [Silufol; benzene–methanol (1:1)]. UV spectrum, λ_{max} ($CHCl_3$): 282, 373, and 410 nm (log ε 5.18, 2.25, and 2.24). IR spectrum: 1525 and 1575 cm^{-1} (C=N). Mass spectrum: m/e 388 (M^+, 1.2%), 233 (M – Ts, 21%), 232 (100%), and 217 (232 – CH_3, 27%). Also obtained was 0.18 g of bis[1-methyl-2-tosylamino-3-indolyl]phenylmethane (VI) with mp 198-199° (from benzene) (mp 199° [5]).

B) A 0.2-g (0.6 mmole) sample of 1-methyl-2-tosylaminoindole and 0.2 g (1.3 mmole) of p-dimethylaminobenzaldehyde were dissolved by heating in 5 ml of alcohol containing hydrogen chloride, after which the mixture was heated for 1 h. The precipitated crystals were separated and washed with aqueous alcohol to give 0.26 g (91%) of red crystals of IVb with mp 146-152°. IR spectrum: C=N (1530 and 1600 cm^{-1}). UV spectrum ($CHCl_3$): λ_{max} 271, 332, and 471 nm (log ε 3.20, 2.41, and 3.18). PMR spectrum ($CDCl_3$): 2.33 (3H, s, $TsCH_3$), 3.43 (3H, s, NCH_3), 3.03 [6H, s, $N(CH_3)_2$], 6.31-8.0 (12H, m, aromatic protons), and 8.61 (1H, s, H_b), Mass spectrum, m/e: 431 (M^+, 16.7%), 276 (M – Ts, 100%), 261 (M – $TsCH_3$, 16.8%), 230 [M – Ts – $N(CH_3)_2$, 9%], 155 ($C_{10}H_7N_2$, 3.3%), 145 (300 – Ts, 60%), and 91 (50%). Found: C 69.8; H 5.7; N 9.5%. $C_{25}H_{25}N_2O_2S$. Calculated: C 70.2; H 5.9; N 9.7%.

3-Benzylideneoxindoles. A mixture of 0.1 g (2.7 mmole) of IIa and 3 ml of an alcohol solution of hydrogen chloride was refluxed for 12 h, after which it was cooled, and 10 ml of hexane was added. The precipitated crystals were separated and recrystallized from hexane to give 0.05 g (85%) of a product with mp 134° (mp 134° [9]). IR spectrum: C=O (1700 cm^{-1}).

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